to an Fc receptor and said protein fragment or peptide comprises a T cell receptor antagonist, said composition having the property of being endocytosed by cells bearing said Fc receptor and processed by the cells to present said T cell receptor antagonist in association with endogenous MHC Class II molecules.

67. The composition of Claim 66, further comprising a pharmaceutically acceptable carrier.

68. The composition of Claim 66, wherein said protein fragment or peptide comprising the T cell receptor antagonist is directly linked to said immunoglobulin or portion thereof via a linkage selected from the group consisting of noncovalent linkages and covalent linkages.

69. The composition of Claim 68, wherein said T cell receptor antagonist is an analog of a peptide agonist capable of activating a T cell response to proteolipid protein.

70. The composition of Claim 68, wherein said immunoglobulin or portion thereof comprises at least part of a domain of a constant region of an immunoglobulin molecule.

71. The composition of Claim 68, wherein the wherein said composition comprises a complex between said immunoglobulin or portion thereof and said peptide.

72. The composition of Claim 68, wherein the composition is a chimeric antibody in which said protein fragment or peptide comprising said T cell receptor antagnoist is covalently joined to said immunoglobulin or portion thereof in a single molecule.

73. The composition of Claim 72, wherein said protein fragment or peptide comprising said T cell receptor antagonist is positioned within at least one complementarity determining region to partially or fully replace said complementarity determining region.

## REMARKS

I. Examiner Interview

Initially, Applicant wishes to thank Examiner Reeves for the courtesy extended to Chris Dayton, Applicant's representative, and Dr. Catherine Woods during a personal interview on April 22, 1998. The substance of that interview is accurately reflected on the contemporaneous Examiner Interview Summary Record, and is further incorporated into the foregoing amendments and these remarks. Applicant particularly appreciates the efforts of the Examiner directed to clarifying the scope of the present invention and analyzing the breadth and relevance of the cited art.

II. Restriction/Election

In response to the Restriction/Election requirement mailed August 1, 1997, Applicant elected Group I comprising Claims 1-11 and 22-29 for examination with traverse. Group I was drawn to compounds and compositions comprising an Fc receptor ligand and an immunosuppressive factor. Applicant expressly reserves the right to rejoin withdrawn process claims for making and using the compounds and compositions of Group I upon notification of allowable subject matter in the elected invention.

In response to the Restriction/Election requirement mailed August 1, 1997, Applicant also elected the species of "proteolipid protein" upon which presently pending Claims 4, 24, and 69 are readable for examination. Presently pending Claims 6, 8, 9, 11, 24, 26, 27, 29, 66-68, and 70-73 are generic to the elected species. Applicant understands that non-elected species can also be rejoined upon allowance of generic claims.

Except as otherwise permitted under the rights of rejoinder discussed above, Applicant will cancel any claims drawn to non-elected inventions upon notification of allowable subject matter in the elected invention.

III. Objections to the Specification

The specification was objected to because it recited pending applications having Serial Nos. 08/363,276 and WO 94/14847. As it is believed these applications are still pending, the specification has not been amended at this time. Should these applications issue during the pendency of the present application, the specification will be amended accordingly.

IV. Rejections Under 35 U.S.C. §112

Claims 1-4, 6-11, 22-24, and 26-29 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting "immunosuppressive agent" and "immunosuppressive factor." As amended above, the claims do not include this terminology. Rather, Applicant has amended the claims to clarify that the compositions of the present invention comprise a "protein fragment or peptide comprising a T cell receptor antagonist." Direct support for the instant

amendment may be found at page 19, lines 13-24 of the application and throughout the Examples as filed. As such, withdrawal of this rejection is respectfully requested.

Claims 1-4, 6-11, 22-24, and 26-29 were also rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting "an immunomodulating agent." As amended above, the claims do not include this terminology. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 4 and 24 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting "analog." As attested in the accompany Declaration Under 37 C.F.R. §1.132 the terminology "analog" has a well defined meaning to those skilled in the art. As stated in Section 4 of the Declaration, an analog is a peptide which shares significant structural and functional homology with another peptides such as an antigen associated with autoimmune disease but which varies with respect to certain features of the other peptide. As such, it is believed that this rejection may properly be withdrawn.

Claims 6 and 26 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting "at least part of one domain of a constant region" because it was unclear whether that terminology would include a single amino acid from a constant region. Claims 6 and 26 are dependent upon new Claims 66 and 67 which recite that the immunoglobulin or portion thereof is capable of binding to the Fc receptor. Binding properties can readily be measured by a person of ordinary skill in the art. Accordingly, the terminology "at least part of one domain of a constant region" refers to a constant region or a portion thereof which is large enough to be capable of binding to the Fc receptor. Thus, Claims 6 and 26 are not indefinite and withdrawal of this rejection is respectfully requested.

Claim 8 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting that "the immunomodulating agent comprises an antibody-antigen complex" because it was not clear which portion was the immunoglobulin and which portion was the antigen. The above amendments to Claim 8 recite that the compositions comprise a complex between the immunoglobulin and the peptide, thereby removing any ambiguity which may have resulted from this terminology. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 11 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite in reciting "wherein said T cell receptor antagonist is expressed within at least one complementarity

determining region" because it was not clear whether the antagonist replaces the CDR or whether the antagonist is placed within the CDR. As amended above, Claim 11 recites that the T cell receptor antagonist is positioned within at least one complementarity determining region to fully or partially replace the CDR. These amendments are supported in the specification at page 24, lines 15-21 and page 31, line 11 through page 32, line 17.

Claims 9-11 and 29 were rejected under 35 U.S.C. §112 first and second paragraph. The claims were rejected as being indefinite in reciting "chimeric" antibodies. As amended above, Claims 9 and 29 recite that the peptide is covalently joined to said immunoglobulin or portion thereof in a single molecule. The specification recites that the compositions of the present invention may comprise "a single chimeric molecule incorporating both the immunosuppressive factor (i.e. a TCR antagonist) and FcR ligand." (See the specification at page 13, lines 17-18 as well as the portions of the specification cited in the preceding paragraph) Accordingly, these amendments are supported in the specification.

The Examiner also asserted that the specification did not enable chimeric antibodies commensurate with the scope of the claims because only chimeric antibodies having murine variable regions and human constant regions have been contemplated. As discussed above, the term "chimeric" requires that the immunoglobulin or portion thereof and the peptide be present in a single molecule and does not refer to the species from which the portions of the immunoglobulin are derived. However, as described in the specification at page 24, lines 4-7, the immunoglobulin portion of the single molecule may comprise a "humanized" immunoglobulin.

The Examiner also asserted that the specification was not enabling for chimeric antibodies because modifications of the variable region may affect the specificity and affinity of the antibody. In the chimeric antibodies of the present invention, the specificity and affinity of the antibody for its target antigen are not material. In the chimeric antibodies of the present invention, the peptide is covalently linked to the immunoglobulin or portion thereof rather than being linked via a noncovalent interaction with the antigen binding site of the immunoglobulin. As antigen recognition is not required for the activity of such chimeric proteins, the effects of modification of the CDR upon antigen recognition and affinity are immaterial.

Claims 1-4, 6-11, 22-24 and 26-29 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not enabled by the specification. The Examiner asserted that

the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody and that minor variations in the amino acid sequences of the light and heavy chains may dramatically affect antigen-binding function. As discussed above, in the chimeric antibodies of the present invention, the ability of the antibody to recognize an antigen is immaterial. Thus, the rejection is not believed to be applicable.

However, the Examiner will appreciate that in compositions in which the immunoglobulin and protein fragment or peptide form a complex, such as those recited in Claim 8, the antibody may retain sufficient specificity to allow it to recognize the peptide antigen. The generation of such complexes is within the ability of those of skill in the art, as such complexes may be formed using antibodies having unmodified antigen-binding regions or using modified or humanized antibodies prepared using well known genetic engineering techniques.

Claims 22-24 and 26-29 were rejected under 35 U.S.C. §112, first paragraph because the Examiner asserted that the enablement of a "pharmaceutical composition" requires a teaching of "*in vivo* administration for purposes consistent with the intended use disclosed in the specification." The specification describes the administration of the claimed compositions in a carrier of PBS/CFA and thus teaches the *in vivo* administration of the claimed compositions in a pharmaceutically acceptable carrier to inhibit the T cell response (See Example XI). In addition, Applicant has provided a list of pharmaceutical carriers which may be used to formulate the claimed compositions. (See specification on page 23, lines 19-30.) The preparation and administration of active agents in these pharmaceutical carriers is well known to those of skill in the art. Furthermore, Applicant notes that patentability does not hinge on a showing that the claimed compositions are effective in treating autoimmune diseases in humans. (See the following discussion of *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).)

The Examiner asserts that the specification is not enabling because it fails to teach the dosage which constitutes an "effective amount" of the claimed compositions for treating immune disease. The specification discloses the amount of the claimed compositions which was effective in inhibiting the T cell response to the corresponding agonist in a standard animal model. (See Example XI) Furthermore, the specification provides a range of dosages for administering the claimed compositions. (See specification on page 27, lines 4-12.) As stated in the specification, the appropriate dosages may be determined by conducting standard clinical trials. However,

Applicant notes that, as stated in *In re Brana,* "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." *In re Brana, supra* at 1442. Furthermore, as discussed in more detail below, Applicant notes that patentability of the claimed compositions does not require a demonstration that the compositions are effective in treating autoimmune disease in humans.

Citing Sercarx et al., the Examiner asserts that the specification is not enabling because immunosuppression via endocytic presentation of T cell antagonists is unpredictable. The claims no longer recite immunosuppression so this ground of rejection is no longer applicable. Furthermore, in the present case, the specification enables the claimed compositions because no experimentation beyond routine experimentation is required to practice the claimed invention. The mere fact that some experimentation is required to determine whether a peptide is an effective T cell antagonist does not render the specification non-enabling. *In re Wands,* 8 U.S.P.Q.2d at 1404 (Fed. Cir. 1988) As stated in *In re Wands,* 8 U.S.P.Q.2d at 1404 (Fed. Cir. 1988), "enablement is not precluded by the necessity for some experimentation such as routine screening." The *Wands* decision cited *In re Jackson*, 217 U.S.P.Q. at 807 (Bd. Pat. App. & Int., 1982) where it was stated "The test is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Thus, in *Wands*, the Federal Circuit found that, because the screening and generation of hybridomas was routine, claims to high affinity monoclonal antibodies were enabled despite the fact that many hybridomas would have to be screened to obtain the claimed monoclonals.

In the present case, the specification describes methods for constructing, characterizing, and determining the efficacy of the claimed compositions. For example, the specification provides methods for generating compositions comprising an immunoglobulin or portion thereof capable of binding to the Fc receptor and a T cell receptor antagonist. (See Examples I and II.) Example V describes methods for confirming that the T cell receptor antagonist is present on chimeric antibodies. Example VIII describes methods for analyzing the ability of the claimed composition to inhibit T cell activation *in vitro.* Example XI describes methods for evaluating the ability of the claimed compositions to inhibit T cell activation *in vivo.* Thus, using the disclosure in the

specification, one skilled in the art can construct, identify and evaluate the efficacy of the claimed compositions.

Furthermore, as attested in Section 6 of the accompanying Declaration, methods for identifying epitopes associated with autoimmune diseases, generating analogs of these epitopes, and characterizing the ability of these epitopes to inhibit T cell activation are within the ability of those skilled in the art. In this respect Applicant notes that application WO 96/16086, discussed in the paragraph bridging pages 9 and 10, provides methods for identifying T cell receptor antagonists compatible with the teachings of the present invention. As in *In re Wands, supra,* the fact that routine screening procedures are required to generate and identify analogs which act as antagonists does not render the specification non-enabling.

The Examiner cites Sebzda for the propositions that the specification is not enabling because the same peptide can both positively and negatively select T cells and that whether the event is immunosuppressive or immunoenhancing is dependent upon the numbers of TCRs engaged with MHC molecules at a given time. The Sebzda reference relates to thymic selection of immature T cells, a process by which T cells which recognize self antigens are deleted and never mature. Thymic selection is irrelevant to the operation of the present invention. Instead, the present invention relates to the inhibition of the activity of mature peripheral T cells which have avoided deletion and which recognize self-antigens. Thus, the compositions of the present invention act at a level downstream from thymic selection. As attested in Section 5 of the accompanying Declaration, thymic selection and the activation of mature T cells are distinct from one another.

The Examiner also cites references by Jameson, Hsu, Feldman, and Evavold to support the assertion that the specification is not enabling. Hsu and Jameson relate to thymic selection and are believed to be immaterial for the reasons discussed above.

Each of the Evavold references describe the production of peptide analogs which have distinct consequences on T cell activity from the native peptides. Accordingly, rather than teaching the unpredictability of the present invention, these references support the fact that the generation of peptide analogs and the evaluation of their effects on T cell activity are routine procedures which are readily implemented by those skilled in the art.

Feldman et al. indicates that nonspecific T cell regulation using previous methods may not be effective in treating late stage rheumatoid arthritis because the previous methods downregulate both the pathogenic T cell functions and the protective T cell functions. In contrast, Applicant's method is a specific approach in which the activity of T cells which recognize a peptide responsible e.g. for the pathogenic state are downregulated without downregulating the activity of T cells in general. Furthermore, Applicant has demonstrated that the claimed invention effectively inhibits T cell activity in a standard animal model. Thus, the fact that the alternative approaches described in Feldman were ineffective does not render the present invention unpredictable. Accordingly, Feldman et al. does not render the specification non-enabling for the claimed invention.

Jameson et al. indicates that some cases involving polyclonal T cell responses are difficult to antagonize. However, citing articles relating to autoimmune encephalitis, human allograft rejection, experimental allergic encephalitis, and lymphocytic choriomenigitis, Jameson states "On the other hand, T cell responses of less diversity, as have been reported in several cases ....., may be very susceptible to antagonism." (Jameson, pg. 1548, paragraph (d), last sentence.) Accordingly, rather than demonstrating the unpredictability of the present invention, Jameson supports the efficacy and applicability of the claimed compositions.

For the reasons discussed above, the cited references do not render the specification non-enabling. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

The Examiner asserts that the specification is not enabling because it does not provide sufficient guidance to enable the skilled artisan to link the use of the claimed compositions and the suppression of an immune response. As discussed above, the claims no longer require suppression of an immune response. Further, Applicant has demonstrated the efficacy of the claimed compositions in standard animal models. As the Federal Circuit held in *In re Brana, supra*, the demonstration of activity in standard animal models is sufficient to satisfy §112 and Applicant need not conduct clinical trials or demonstrate efficacy in humans as a condition of patentability.

The Examiner further asserts that the specification is non-enabling because the skilled artisan is presented with a multitude of diseases against which the pharmaceutical composition must be evaluated with few facts upon which a prediction of efficacy can be made. The claims no longer recite a "pharmaceutical composition"; thus, the rejection is inapplicable. Furthermore, the specification sets forth a variety of autoimmune diseases for which the claimed compositions may

be used. As attested in Section 6 of the accompanying Declaration, those skilled in the art are capable of selecting a T cell antagonist which is often the target of the autoimmune reaction for the disease from which the subject suffers and utilizing a T cell antagonist for that target in the claimed compositions. For example, if the subject suffers from multiple sclerosis, a T cell antagonist for proteolipid protein or myelin basic protein may be employed.

The Examiner also asserts that the specification is non-enabling because the Applicant has not demonstrated the effectiveness of the claimed compositions in humans. Human therapy is not currently claimed. Furthermore, Applicant need not demonstrate efficacy in humans as a condition of patentability. In *In re Brana* the Federal Circuit recently stated "Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *In re Brana*, 34 U.S.P.Q.2d 1436,1442 (Fed. Cir. 1995). The Federal Circuit cited the following passage from *In re Krimmel*: "[I]t is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art even though it may eventually appear that the compound is without value in the treatment of humans." *In re Krimmel* 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961). The Federal Circuit continued: "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana, supra* at 1442.

As attested in Section 7 of the accompanying Declaration, Applicant has obtained statistically significant results in a standard animal model for autoimmune disease. Accordingly, Applicant has satisfied the requirements of §112 and withdrawal of this rejection is respectfully requested.

In addition, Applicant notes that the present compositions may be used in contexts other than human therapy, such as in *in vitro* models for studying the presentation of antigens associated with autoimmune diseases. (See the specification, page 36, line 21-page 38, line 17) Again, the claims do not require human therapeutic results and applicant need not prove results that are not claimed.

The Examiner cites Livingstone in support of the proposition that the characterization of a peptide as an agonist or an antagonist is arbitrary. As attested in Section 6 of the accompanying Declaration, since the publication of Livingstone in 1987, numerous altered peptides have been constructed and characterized. Furthermore, as discussed above, the specification provides examples of *in vitro* and *in vivo* techniques for evaluating whether a particular peptide is an effective antagonist of the T cell receptor. The fact that the identification of peptides which act as antagonists of the T cell receptor may require routine screening and evaluation does not negate the patentability of the claimed compositions. *In re Wands, supra.*

The Examiner asserts that the specification is not-enabling because it does not disclose how to use the claimed compositions in humans. As discussed above, Applicant need not demonstrate efficacy in humans as a condition of patentability. *In re Brana, supra.* Furthermore, as discussed above, the claimed invention is useful in contexts other than human therapy.

The Examiner cites Hurtenbach for the proposition that the administration of peptides may be accompanied by negative side effects. As described in the specification, the linkage of the T cell receptor antagonists to an immunoglobulin or portion thereof which is capable of binding the Fc receptor enables the peptide to be directed to the T cell receptor more efficiently, thus reducing the dosage and frequency of administration required with the claimed compositions in comparison to peptides alone. The increased efficiency of the claimed compositions relative to that of peptides alone is supported by Examples VII, VIII, and XI. Accordingly, the present compositions may reduce such side effects. Further, there is no legal basis for the proposition that a useful composition is unpatentable because of side effects.

The Examiner asserts that the specification is non-enabling because it fails to provide a correlation between the results obtained in the animal model and the results expected in humans. Human therapy is not claimed. Further, as attested in Section 7 of the accompanying Declaration, the SJL mouse is a standard animal model used to study autoimmune disease. As discussed above, §112 does not require a demonstration of efficacy in humans. *In re Brana, supra.* Rather, studies conducted in a recognized animal model are sufficient. *Id.*

The Examiner cites Kuchroo et al. in support of the proposition that studies evaluating the results obtained with TCR antagonists in SJL mice demonstrate a disparity between histological improvement and clinical improvement. Applicant notes that Kuchroo et al. describes the

identification of a PLP analog which blocks the induction of disease or progression of disease when administered at the first clinical signs of the disease. In this regard, Kuchroo supports the efficacy of the present invention.

Furthermore, although Kuchroo notes that in some mice there was a disparity between histologic lesions (inflammatory foci) and clinical symptoms, Applicant notes that one application of the present compositions is to relieve clinical symptoms. The claims do not require the elimination of inflammatory foci. Compositions which alleviate clinical symptoms are valuable even if inflammatory foci are not completely eliminated. Applicant has demonstrated that the claimed compositions may be used to inhibit T cell activation *in vivo* in a standard animal model. As discussed above and in the accompanying Declaration, *In re Brana* provides that such a demonstration is sufficient to enable the claimed compositions.

The Examiner asserted that undue experimentation would be required to determine which antagonists may be administered to a particular individual for treatment of an autoimmune disease. As certain epitopes of target self antigens are regularly involved in autoimmune diseases, those skilled in the art are able to identify candidate self antigens which may be associated with autoimmune disease. As described above, and attested in Section 6 of the accompanying Declaration, those skilled in the art are able to identify epitopes involved in autoimmune disease, design analogs of these epitopes, and identify those analogs which act as TCR antagonists using routine techniques. Accordingly, the specification complies with the requirements of §112 in this regard. (*In re Wands, supra*).

The Examiner asserts that the specification is non-enabling because there is no definition of the minimal TCR antagonist. As described above and attested in the accompanying Declaration, those skilled in the art are able to identify epitopes involved in autoimmune disease, design analogs of these epitopes, and identify those analogs which act as TCR antagonists using routine techniques. (*In re Wands, supra*)

The Examiner cites Ashton-Rickardt et al. for the proposition that the substitution of just one amino acid has the potential either to abolish or to reduce the ability of a peptide to select. Ashton-Rickardt relates to thymic selection rather than to the activity of mature T cells in the periphery. As discussed above, thymic selection acts on immature T cells and is not material to the action of the present invention on mature T cells.

The Examiner also cites Rudikoff et al in support of the non-enablement rejection. As discussed above, Rudikoff relates to the affinity of an antibody for an antigen. As discussed above, in the chimeric antibodies of the present invention, the peptide is not bound to the antibody through noncovalent interactions with the antigen binding site but is instead covalently linked to the immunoglobulin. For the presently claimed chimeric antibodies, the affinity of the antibody for an antigen is completely beside the point. Furthermore, as discussed above, in those compositions in which the antigen and the antibody form a complex, the peptide may be bound to the antigen binding site through non-covalent interactions. However, the generation of such complexes is within the ability of those skilled in the art since such complexes may be formed using antibodies having unmodified antigen binding regions or using modified or humanized antibodies prepared using well known genetic engineering techniques. Accordingly, the specification complies with the requirements of §112, and withdrawal of this rejection is respectfully requested.

For the reasons discussed above, the specification enables those skilled in the art to identify TCR antagonists and to construct compositions in which the TCR antagonists are linked to an immunoglobulin or portion thereof which is capable of binding the Fc receptor. Accordingly, since the specification complies with the requirements of §112, Applicant respectfully requests withdrawal of the above rejections.

V. Rejections Under 35 U.S.C. §103

Claims 1-4, 6-11, 22-24, and 26-29 were rejected under 35 U.S.C. §103 over the combination of Kuchroo et al. (J. Immunol. 148:3776-3782), Mueller et al. (WO 96/34622), Zanetti (WO 94/14847), Zanetti (5,508,386), Kappler et al. (WO 95/23814), Selick et al. (WO 93/10220) and Bona et al. (Cellular and Molecular Biology 40: 21-30).

The compositions of the present invention are not obvious over the cited combination. In order to be obvious over the cited combination of references, the references must provide both a motivation to combine the references to achieve the claimed invention and a reasonable expectation that the claimed invention would be successful if produced. (See *Panduit Corp. v. Dennison Mfg. Co.*, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987); *ACS Hospital Sys., Inc. v. Montefiore Hospital* 221U.S.P.Q. 929 (Fed. Cir. 1984); *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). Because the

cited combination of references fails to meet these criteria, Applicant submits that the presently claimed invention is not obvious.

Kuchroo et al. describes synthetic peptides comprising residues 139-141 of the myelin proteolipid protein. Applicant notes that there is absolutely no disclosure regarding the use of T cell receptor antagonists for any purpose. Moreover, there is no disclosure or suggestion to link the disclosed peptides to immunoglobulins or portions thereof to construct compositions in which the Fc binding portion of the immunoglobulin directs endocytosis of the peptide such that the peptide is presented in association with endogenous MHC Class II molecules.

Similarly, Mueller et al., while disclosing a variety of proteolipid peptides, fails to disclose or suggest the use of T cell receptor antagonists. Further, this reference does not disclose or suggest linking the disclosed peptides to immunoglobulins to construct compositions in which the Fc binding portion of the immunoglobulin directs endocytosis and presentation of the associated peptide.

Zanetti et al. (both U.S. Patent No. 5,508,386 and WO 94/14847) disclose the insertion of non-self antigens derived from microorganisms into the CDR of an antibody. Again, there is absolutely no suggestion that T cell receptor antagonists could be utilized in any manner, much less that they could be used as taught in the instant application. Rather, Zanetti is primarily concerned with immunization (in which an immune response is stimulated as opposed to the inhibition of an immune response as in the present invention), although there is speculation that self antigens may be inserted into the CDR to tolerize. As attested in Section 8 of the accompanying Declaration, tolerance is mediated by a different population of cells (non-professional APCs) than the population of cells which endocytose antigens and present them in the context of MHC Class II molecules (professional APCs). Accordingly, the suggestion in Zanetti that antibodies containing self-antigens can tolerize does not suggest or disclose the mechanism through which the present compositions act (endocytosis and presentation of the peptide in the context of MHC Class II molecules). One seeking to use a tolerization mechanism, as suggested by Zanetti, would actually be led away from the present invention. In addition, neither of the Zanetti references provide any experimental results which indicate that immunoglobulins linked to T cell receptor antagonists are effective in inhibiting T cell activity. Accordingly, these references do not provide a reasonable

expectation that such compositions would be successful if constructed nor do these references enable one skilled in the art to practice the presently claimed compositions.

Bona et al. disclose immunoglobulins carrying antigenic peptides derived from microorganisms. As discussed above with respect to the Zanetti references, Bona is primarily concerned with immunization (in which an immune response is stimulated as opposed to the inhibition of an immune response as in the present invention). Bona et al. also speculate that "it is possible that the Ig bearing epitopes of self antigens will be more efficient for peptide competition therapy envisioned as a novel immunotherapeutic approach of autoimmune diseases" (pg. 29, underlining added). However, Bona et al. does fails to provide any indication that T cell receptor antagonists could be advantageously used to downregulate an autoantigenic response. In this regard the reference certainly does not afford any suggestion whatsoever that immunoglobulins linked to T cell receptor antagonists are effective in inhibiting T cell activity. Accordingly, Bona et al. cannot provide a reasonable expectation that such compositions would be successful if constructed nor, absent improper hindsight, would it enable one skilled in the art to practice the invention using the presently claimed compositions.

Kappler discloses peptides linked to an MHC molecule through a linker. The compositions of Kappler do not bind to the Fc receptor to direct endocytosis and presentation of the peptide via endogenous MHC molecules as do the compositions claimed herein. Rather, in the compositions of Kappler, the MHC molecule is an exogenous molecule. Accordingly, Kappler does not disclose or suggest linking T cell antagonist peptides to an immunoglobulin or portion thereof nor does it disclose or suggest presentation of the peptide via an endogenous MHC protein. In addition, Kappler does not provide any experimental data indicative that compositions which bind to APCs via the Fc receptor and are endocytosed to present the peptide in the context of an endogenous MHC protein are effective. Thus, Kappler does not provide a reasonable expectation that the presently claimed compositions would be successful, nor does it enable one skilled in the art to practice the presently claimed invention.

Likewise, the compositions of Selick contain an exogenous MHC protein. Furthermore, Selick provides no experimental data indicative that the compositions disclosed therein are effective in inhibiting the immune response, nor does it disclose or suggest that compositions which bind to APCs via the Fc receptor and are endocytosed to present the peptide in the context of an

endogenous MHC protein are effective. Accordingly, Selick does not provide a reasonable expectation that the presently claimed compositions would be effective, nor does it enable one skilled in the art to practice the presently claimed invention.

For the above reasons, the cited combination of references do not provide both a motivation to combine the references to achieve the claimed invention and a reasonable expectation that the claimed invention would be successful if produced.

VI. Conclusion

In view of the foregoing, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested. Should the Examiner have any questions regarding this matter he is invited to telephone the undersigned so that the questions may be resolved.

Respectfully submitted,

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Dated: 6-1-98

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